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ORIGINAL REPORT

HLA-Identical Sibling Compared With 8/8 Matched and Mismatched Unrelated Donor Bone Marrow Transplant for Chronic Phase Chronic Myeloid Leukemia

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ABSTRACT

Purpose
Transplantation of hematopoietic stem cells from an unrelated donor (URD) is an option for many patients who do not have an HLA-identical sibling donor (MSD). Current criteria for the selection of URDs include consideration for HLA alleles determined by high resolution typing methods, with preference for allele-matched donors. However, the utility and outcome associated with transplants from URDs compared with those from MSDs remains undefined.

Patients and Methods
We examined clinical outcome after patients received bone marrow transplants (BMTs) from MSDs; HLA-A, -B, -C, and DRB1 allele-matched URDs (8/8); and HLA-mismatched URDs in a homogeneous population of patients with chronic myeloid leukemia (CML) in first chronic phase (CP1) where a strong allogeneic effect and hence a lower risk of relapse is anticipated. Transplantation outcomes were compared between 1,052 URD and 3,514 MSD BMT recipients with CML in CP1.

Results
Five-year overall survival and leukemia-free survival (LFS) after receipt of BMTs from 8/8 matched URDs were worse than those after receipt of BMTs from MSDs (5-year survival, 55% *v* 63%; RR, 1.35; 95% CI, 1.17 to 1.56; $P < .001$; LFS, 50% *v* 55%; RR, 1.21; 95% CI, 1.06 to 1.40; $P = .006$). Survival was progressively worse with greater degrees of mismatch. Similar and low risk of relapse were observed after receipt of transplant from either MSD or URD.

Conclusion
In this homogeneous cohort of good risk patients with CML in CP1, 5-year overall survival and LFS after receipt of transplant from 8/8 allele-matched donors were modestly though significantly worse than those after receipt of transplant from MSDs. Additive adverse effects of multilocus mismatching are not well tolerated and should be avoided if possible.

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INTRODUCTION

Despite recent advances in therapy, allogeneic hematopoietic cell transplantation (HCT) still remains the only known curative option for chronic myeloid leukemia (CML).[1] Transplants from HLA-identical siblings (MSDs) have been associated with the most favorable outcomes.[2-4] However, MSDs are available for only one third of the patients. Transplants from alternative donors including unrelated donors (URDs), cord blood, or mismatched related donors[5-12] are frequently used in such cases, particularly if tyrosine kinase inhibitors fail to produce a sustained cytogenetic remission or if the disease progresses to more advanced stage.[13,14] Of these alternatives, URD HCT is most widely accepted. The level of HLA matching in selection[15] process has changed over time, with high resolution allele level matching for HLA class I and DRB1 loci being increasingly used in selection criteria.[7,15-24] To investigate the outcomes of URD versus MSD, we performed a comparative analysis of clinical outcomes in a homogeneous cohort of patients receiving bone marrow transplants (BMTs) from MSDs, and 8/8 allele-matched and -mismatched URDs for treatment of CML in first chronic phase (CP1).

PATIENTS AND METHODS

Center for International Blood and Marrow Transplant Research (CIBMTR) is a research organization formed in 2004 through an affiliation between the International

Table 1. Demographics and Clinical Characteristics of Patients With CML in CP1 Who Received a Myeloablative MSD or URD BMT

Variable	MSD		8/8 URD		< 8/8 URD		*P*
	No.	%	No.	%	No.	%	
No. of patients	3,514		531		521		
No. of centers	266		87		87		
Median age, years	36		37		35		.0008
Range	2-66		3-58		1-60		
Age at transplantation, years							
0-19	302	9	49	9	77	15	
20-39	1,900	54	258	49	261	50	
> 40	1,312	37	224	42	183	35	
Recipient race							< .0001
White	2,648	75	496	93	413	79	
Black	279	8	8	2	44	8	
Hispanic	100	3	16	3	39	7	
Other	487	14	11	2	25	5	
Sex, male	2,095	60	299	56	283	54	.04
Karnofsky prior to transplant > 90%	3,149	90	474	90	468	91	.98
Donor type and HLA matching							NA
HLA-identical sibling	3,514	100	0		0		
8/8 matched URD	0		531	100	0		
7/8 matched URD	0		0		252	48	
6/8 matched URD	0		0		158	30	
< 6/8 matched URD	0		0		111	22	
Median time from diagnosis to transplantation, months	9		11		15		< .0001
Range	< 1-206		3-213		2-154		
Time from diagnosis to transplantation, years							< .0001
< 1	2,182	62	280	53	185	36	
1-2	864	25	139	26	175	34	
> 2	468	13	112	21	161	31	
Donor/recipient sex match							.002
Male/male	1,190	34	202	38	173	33	
Male/female	746	21	126	24	120	23	
Female/male	905	26	97	18	110	21	
Female/female	673	19	106	20	118	23	
Donor/recipient CMV match							< .0001
Negative/negative	857	24	200	38	157	30	
Negative/positive	462	13	136	26	156	30	
Positive/negative	401	11	83	16	91	17	
Positive/positive	1,599	46	95	18	100	19	
Unknown	195	6	17	3	17	3	
Conditioning including TBI	1,578	45	442	83	432	83	< .0001
GVHD prophylaxis							< .0001
Tacrolimus ± other	40	1	75	14	58	11	
CsA + MTX ± other	2,646	75	349	66	315	60	
CsA ± other (no MTX)	504	14	21	4	18	3	
MTX ± other (no CsA)	33	1	4	1	10	2	
T-cell depletion	261	7	80	15	119	23	
Other	30	1	2	< 1	1	< 1	
Year of transplantation							< .0001
1988-1992	1,761	50	91	17	117	22	
1993-1997	1,343	38	232	44	213	41	
1998-2003	410	12	208	39	191	37	
Prior therapy							
Busulfan/hydroxyurea + interferon + cytarabine	918	26	11	2	4	< 1	< .0001
Busulfan/hydroxyurea + cytarabine	2,344	67	435	82	447	86	
Interferon	115	3	1	< 1	2	< 1	
Imatinib + other	12	< 1	15	3	8	2	
Other	125	4	69	13	60	12	

(continued on following page)

Table 1. Demographics and Clinical Characteristics of Patients With CML in CP1 Who Received a Myeloablative MSD or URD BMT (continued)

Variable	MSD No.	MSD %	8/8 URD No.	8/8 URD %	< 8/8 URD No.	< 8/8 URD %	*P*
EBMT score							< .0001
0-1	1,122	32	28	5	31	7	
2	1,508	43	133	25	106	20	
3	772	22	211	40	216	41	
≥ 4	112	3	159	30	168	32	
Median follow-up of survivors, months	97		108		103		
Range	2-209		12-219		8-216		< .0001

Abbreviations: CML, chronic myeloid leukemia; CP1, first chronic phase; MSD, HLA-identical sibling donor; 8/8 matched URD, unrelated donor allele level matched at HLA-A, -B, -C, and -DRB1; < 8/8 URD, mismatched unrelated donor; BMT, bone marrow transplant; NA, not assessable; 7/8 matched URD, single mismatch at antigen or allele level at HLA-A, -B, -C or allele level mismatch at DRB1; 6/8 matched URD, double mismatch at antigen or allele level at HLA-A, -B, -C or allele level mismatch at DRB1; < 6/8 matched URD, more than two mismatches at antigen or allele level at HLA-A, -B, -C or allele level mismatches at DRB1; CMV, cytomegalovirus; TBI, total body irradiation; GVHD, graft-versus-host disease; CsA, cyclosporine; MTX, methotrexate; EBMT, European Group for Blood and Marrow Transplantation.

Bone Marrow Transplant Registry (IBMTR), the Autologous Blood and Marrow Transplant Registry (ABMTR), and the National Marrow Donor Program (NMDP). The CIBMTR is a voluntary organization involving more than 500 transplant centers that have collaborated to share patient data and conduct scientific studies. Participating transplant centers are required to report all consecutive transplantations to a Statistical Center at the Medical College of Wisconsin or NMDP Coordinating Center in Minneapolis. Quality and compliance of data submission are monitored by computerized check for errors, physician reviews, and on-site audits. Observational studies conducted by CIBMTR are done with a waiver of informed consent and in compliance with Health Insurance Portability and Accountability Act (HIPAA) regulations as determined by institutional review board and privacy officer of the Medical College of Wisconsin.

HLA Typing

For URDs and recipients, high-resolution typing was performed for HLA-A, -B, -C, -DRB1, -DQA1, -DQB1, -DPA1, and -DPB1, as described.[15,24] Directional mismatches were considered in analysis of graft-versus-host disease (GVHD) as described.[19] For URD recipient pairs, high-resolution HLA matching at HLA-A, -B, -C, and -DRB1 was defined as 8/8 allele level matching. Recipients of MSD transplants were confirmed to be HLA identical with their sibling donor through family study.

Patient Selection

Patients with CML in CP1 who received a first BMT from MSD or URD (with high-resolution typing available at HLA-A, -B, -C, and -DRB1) using myeloablative preparative regimen between 1988 and 2003 were eligible. All surviving recipients who received transplants from URDs included in this analysis were retrospectively contacted and provided informed consent for participation in the NMDP research program. Informed consent for retrospective data analysis was waived by NMDP institutional review board for all deceased patients. Surviving patients who did not provide signed informed consent to allow analysis of their clinical data were excluded. To adjust for potential bias introduced by exclusion of nonconsenting surviving patients, a corrective action plan (CAP)–modeling process randomly excluded approximately the same percentage of deceased patients using a biased coin randomization with exclusion probabilities based on characteristics associated with not providing consent for use of data in survivors.

Study End Points

The primary end points were overall survival and leukemia-free survival (LFS). Secondary end points included relapse (hematologic or cytogenetic), transplant related mortality (TRM), grade 2 to 4 acute GVHD, and chronic GVHD. Acute GVHD was graded according to consensus criteria.[25] TRM was defined as death within first 28 post-transplant days or death while continuously free of relapse or progression. LFS was defined as survival without disease progression or relapse; patients alive without disease progression or relapse were censored at the time of last follow-up. Overall survival was defined as death from any cause and surviving patients were censored at date of last contact.

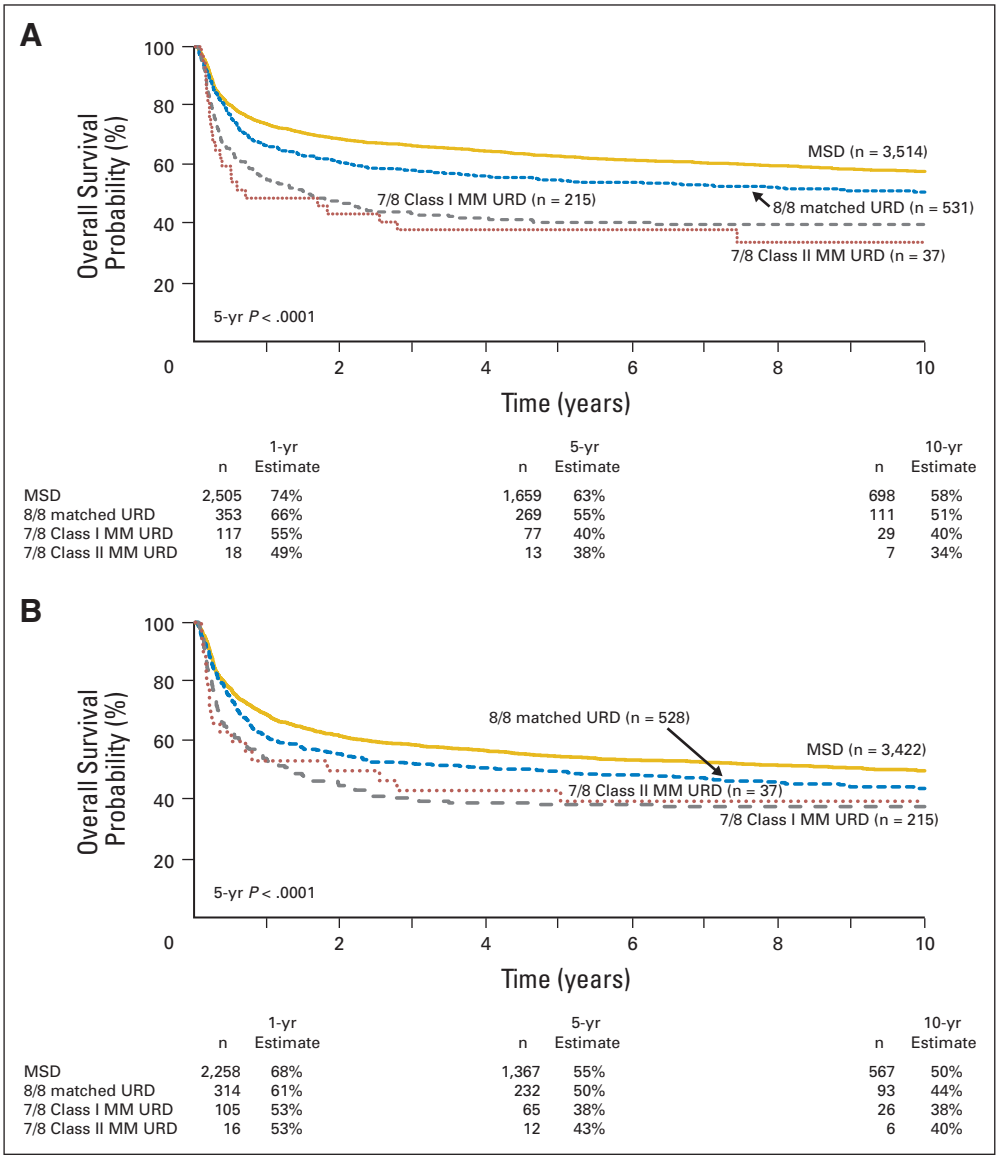
Statistical Analysis

Variables related to patient, disease, and transplant characteristics were compared using χ^2 test for categoric variables and Kruskal-Wallis test for continuous variables. A risk score for all patients was generated using main pretransplant risk factors identified in previous studies and reported to the European Group for Blood and Marrow Transplantation.[26] Cumulative incidence for TRM was calculated treating disease progression/relapse as competing risk and cumulative incidence for disease progression/relapse was calculated treating TRM as competing risk. Similarly, death was a competing risk for the cumulative incidence for chronic GVHD and grade 2 to 4 acute GVHD.[27] LFS and overall survival were calculated based on Kaplan-Meier estimates and the 95% CIs were calculated using the variance derived from Greenwood's formula.[28] We used log-rank test to compare the difference between groups in the time-to-event analyses and χ^2 or Fisher's exact tests for proportions. All *P* values were two sided.[29]

Patient-related, disease-related, and treatment-related variables were included in the multivariate analyses using a stepwise forward selection technique and $P \leq .01$ was the criterion for inclusion in final models. Patient-related variables included recipient age, race, and performance status. Transplant-related variables included in the model were: HLA matching (MSD *v* 8/8 allele-matched URD *v* 7/8 class I mismatched URD *v* 7/8 DRB1 mismatched URD *v* 6/8 class I mismatched URD *v* 6/8 mixed mismatched URD [single class I + single HLA DRB1]), donor age at transplantation, donor-recipient sex mismatch, donor-recipient cytomegalovirus serology, conditioning regimen, GVHD prophylaxis, and year of transplantation. Disease-related variables included time from diagnosis to transplantation. The main factor being tested in this study was the effect of HLA matching on clinical end points; therefore, this variable was included in all models. This study evaluates comparative outcomes after receipt of transplants from MSDs and URDs in a homogeneous population of CML in CP1, with high-resolution typing available. The clinical significance of locus specific mismatches was not the focus of the current study because two recent CIBMTR analyses have addressed these HLA questions in larger transplant populations.[13,22] Insufficient numbers within each group of single locus mismatch were available to repeat this evaluation.

RESULTS

The study cohort included 3,514 MSD and 1,052 URD transplant recipients. Of the URD transplant recipients, 531 were 8/8 matched



	1-yr n	1-yr Estimate	5-yr n	5-yr Estimate	10-yr n	10-yr Estimate
MSD	2,505	74%	1,659	63%	698	58%
8/8 matched URD	353	66%	269	55%	111	51%
7/8 Class I MM URD	117	55%	77	40%	29	40%
7/8 Class II MM URD	18	49%	13	38%	7	34%

	1-yr n	1-yr Estimate	5-yr n	5-yr Estimate	10-yr n	10-yr Estimate
MSD	2,258	68%	1,367	55%	567	50%
8/8 matched URD	314	61%	232	50%	93	44%
7/8 Class I MM URD	105	53%	65	38%	26	38%
7/8 Class II MM URD	16	53%	12	43%	6	40%

Fig 1. (A) Probability of overall survival and (B) leukemia-free survival after receipt of bone marrow transplant. MSD, HLA-identical sibling; 8/8 matched URD, unrelated donor allele level matched at HLA-A, -B, -C, and -DRB1; 7/8 class I MM, single mismatch at antigen or allele level at HLA-A, -B, or -C; 7/8 class II MM, single mismatch at allele level at HLA-DRB1.

at allele level for HLA-A, -B, -C, and -DRB1 (50%), 252 were mismatched for one HLA determinant (24%), and 269 were mismatched for two or more (26%). Of the class I mismatched pairs, 215 had one and 128 had two class I HLA mismatches at either the antigen or allele level. Of mismatches involving HLA-DRB1, 37 had a single allele level mismatch at HLA-DRB1, 28 had a single class I antigen or allele level mismatch and a single allele level HLA-DRB1 mismatch (henceforth, "mixed mismatch"), and only two recipients had two allele mismatches at HLA-DRB1. One hundred eleven patients had more than two mismatches. The clinical characteristics are presented in Table 1. Patients receiving transplants from URDs (8/8 allele matched and < 8/8 matched) were more likely to undergo transplantation using total body irradiation–based conditioning (83% *v* 45%) and also more likely to receive T-cell depletion (19% *v* 7%) than were those receiving transplants from MSDs. They were also more likely to receive a transplant more than 1 year from diagnosis (55% *v* 38%).

Overall Survival

As shown in Figure 1A, probability of overall survival at 5 years was highest in MSD transplant recipients (63%; 95% CI, 61% to 64%) followed by 8/8 matched URD transplant recipients (55%; 95% CI, 51% to 59%). Survival was lower with single class I or II mismatch (40%; 95% CI, 34% to 47%; 38%; 95% CI, 23% to 54%), double class I mismatched (34%; 95% CI, 26% to 43%), or mixed mismatch (21%; 95% CI, 9% to 38%; $P < .0001$). In the multivariate analysis (Table 2), the risk of mortality was 1.35 times (95% CI, 1.17 to 1.56) higher in 8/8 matched URD than in MSD transplant recipients, and progressively worse with greater degrees of mismatch. No difference in the risk of mortality was seen between a single class I versus a single DRB1 mismatch.

Relapse

The cumulative incidence of hematologic or cytogenetic relapse was low and similar in MSD and URD transplant recipients (Fig 2A).

Table 2. Multivariate Analysis: Overall Survival and Leukemia-Free Survival

Donor	No.	Relative Risk	95% CI	*P*	5-Year Survival Estimate (%)
Overall survival*					
HLA-identical sibling	3,514	1.00	—	—	63
8/8 matched URD	531	1.35	1.17 to 1.56	< .0001	55
7/8 class I mismatch	215	1.92	1.58 to 2.33	< .0001	40
7/8 DRB1 mismatch	37	2.08	1.38 to 3.13	.0005	38
6/8 class I mismatch	128	2.53	2.01 to 3.17	< .0001	34
6/8 mixed mismatch (single DRB1 + single class I mismatch)	28	3.17	2.07 to 4.84	< .0001	21
7/8 DRB1 *v* 7/8 class I	NA	1.08	0.70 to 1.68	NS	NA
Leukemia-free survival†					
HLA-identical sibling	3,422	1.0			55
8/8 matched URD	528	1.21	1.06 to 1.40	.006	50
7/8 class I mismatch	215	1.54	1.27 to 1.87	< .0001	38
7/8 DRB1 mismatch	37	1.40	0.89 to 2.19	NS	43
6/8 class I mismatch	128	1.84	1.45 to 2.33	< .0001	35
6/8 mixed mismatch (single DRB1 + single class I mismatch)	28	3.22	2.09 to 4.95	< .0001	20
7/8 DRB1 *v* 7/8 class I	NA	0.91	0.56 to 1.46	NS	NA

NOTE. Shown is the relative risk for death (overall survival) and relapse or death (leukemia-free survival) and associated 95% CIs.

Abbreviations: 8/8 matched URD, unrelated donor allele level matched at HLA-A, -B, -C, and -DRB1; 7/8 class I mismatch, single mismatch at antigen or allele level at HLA-A, -B, or -C; 7/8 DRB1 mismatch, single mismatch at allele level at HLA-DRB1; 6/8 class I mismatch, double mismatch at antigen or allele level at HLA-A, -B; or -C; 6/8 mixed mismatch (single DRB1 + single class I mismatch), double mixed mismatch, includes single mismatch at antigen or allele level at HLA-A, -B, -C, and single allele level mismatch at HLA-DRB1; NA, not assessable; NS, not significant.

*Model for overall survival was also adjusted for each of the following significant variables: cytomegalovirus match, recipient age, time from diagnosis to transplantation, T-cell depletion, year of transplantation, and recipient race; it was stratified on sex mismatch.

†Model for leukemia-free survival was also adjusted for each of the following significant variables: cytomegalovirus match, time from diagnosis to transplantation, T-cell depletion, year of transplantation, sex mismatch, and recipient race; it was stratified on recipient age group.

The 5-year cumulative incidence was 14% (95% CI, 13% to 15%) in MSD transplant recipients, 12% in 8/8 matched URD transplant recipients (95% CI, 9% to 15%), 11% with single class I (95% CI, 7% to 16%), 9% with single DRB1 mismatch (95% CI, 2% to 21%), 7% with two class I mismatches (95% CI, 3% to 12%), and 12% with mixed mismatch (95% CI, 3% to 28%). In the multivariate analysis (Table 3), similar risk of relapse was seen among MSD and matched and mismatched URD transplant recipients. No greater relapse protection was apparent with greater HLA disparity.

TRM

The cumulative incidence of TRM was higher in 8/8 matched URD transplant recipients and progressively increased with increasing degree of mismatch (Fig 2B). The 5-year cumulative incidence of TRM was 31% in MSD transplant recipients (95% CI, 30% to 33%), 38% in 8/8 matched URD transplant recipients (95% CI, 34% to 42%), 50% in presence of single class I mismatch (95% CI, 43% to 57%), 48% with single DRB1 mismatch (95% CI, 31% to 65%), 58% in presence of double class I mismatch (95% CI, 49% to 67%), and 67% in presence of mixed mismatch (95% CI, 48% to 84%; $P < .0001$). In multivariate analysis, risk of TRM with 8/8 matched URD was 1.45 times (95% CI, 1.24 to 1.70) that in MSD transplant recipients and was progressively higher with greater degrees of class I mismatch or mixed mismatch. Single HLA-DRB1 mismatching resulted in a higher risk, but this did not attain statistical significance in this small subset of transplants. No difference in risk of TRM was observed between single class I and single DRB1 mismatch (Table 3).

LFS

The 5-year probability of LFS was 55% in MSD transplant recipients (95% CI, 53% to 56%), 50% in 8/8 matched URD transplant recipients (95% CI, 45% to 54%), 38% with single class I mismatch (95% CI, 32% to 45%), 43% with single DRB1 mismatch (95% CI, 27% to 60%), 35% with double class I mismatch (95% CI, 26% to 44%), and 20% with mixed mismatch (95% CI, 7% to 37%; $P < .0001$; Fig 1B). In multivariate analysis, the risk of death or relapse in 8/8 matched URD transplant recipients was 1.21 times (95% CI, 1.06 to 1.40) that in MSD transplant recipients. A higher risk was seen with single class I, but not single DRB1 mismatch. Double class I mismatch or a mixed mismatch led to an even higher risk. Risk of relapse or mortality was similar between single class I and single DRB1 mismatch (Table 2).

Grade 2 to 4 Acute GVHD

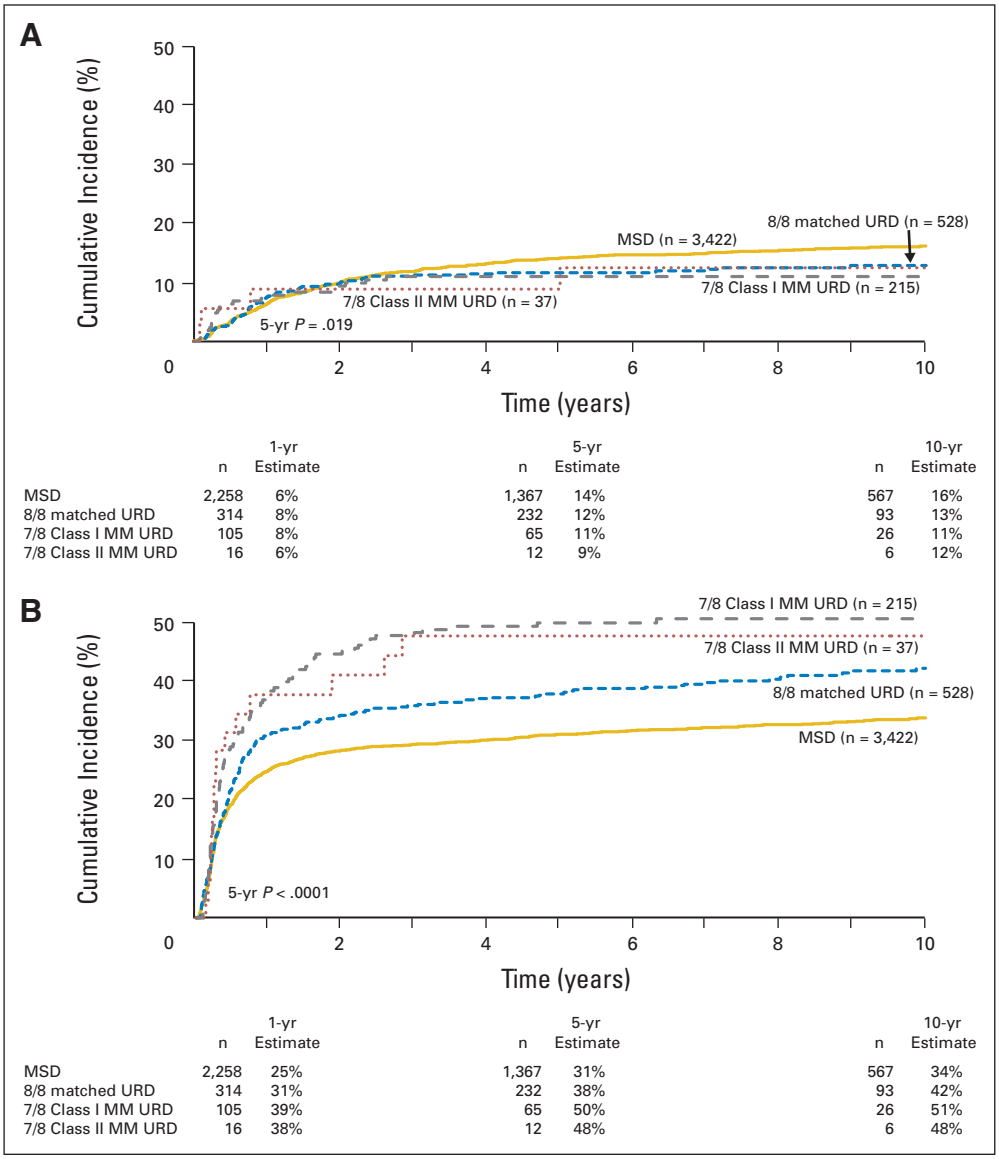
In multivariate analysis (Table 4), risk of grade 2 to 4 acute GVHD was 2.44 times higher in 8/8 matched URD transplant recipients (95% CI, 2.14 to 2.79) than in MSD transplant recipients. The risk was higher in presence of greater degrees of mismatch but was similar between single class I and single DRB1 mismatch.

Chronic GVHD

Risk of chronic GVHD was 1.97 times higher in 8/8 matched URD transplant recipients (95% CI, 1.71 to 2.26) than in MSD transplant recipients (Table 4). Higher risk was observed with single or double class I mismatches but not single DRB1 mismatch. The risk of chronic GVHD was similar between single class I and single DRB1 mismatches.

Time From Diagnosis to Transplantation

Time from diagnosis of CML to transplantation is an important variable which is known to impact outcomes.[3,30] With use of



	1-yr n	1-yr Estimate	5-yr n	5-yr Estimate	10-yr n	10-yr Estimate
MSD	2,258	6%	1,367	14%	567	16%
8/8 matched URD	314	8%	232	12%	93	13%
7/8 Class I MM URD	105	8%	65	11%	26	11%
7/8 Class II MM URD	16	6%	12	9%	6	12%

	1-yr n	1-yr Estimate	5-yr n	5-yr Estimate	10-yr n	10-yr Estimate
MSD	2,258	25%	1,367	31%	567	34%
8/8 matched URD	314	31%	232	38%	93	42%
7/8 Class I MM URD	105	39%	65	50%	26	51%
7/8 Class II MM URD	16	38%	12	48%	6	48%

Fig 2. (A) Cumulative incidence of relapse and (B) treatment-related mortality after receipt of bone marrow transplant. MSD, HLA-identical sibling; 8/8 matched URD, unrelated donor allele level matched at HLA-A, -B, -C, and -DRB1; 7/8 class I MM, single mismatch at antigen or allele level at HLA-A, -B, or -C; 7/8 class II MM, single mismatch at allele level at HLA-DRB1.

imatinib as first-line therapy for newly diagnosed CML, transplantation is being increasingly considered later in the course of the disease. Another factor that may delay transplantation is timely availability of a suitable matched URD. Because more than 90% of the patients selected for this study received transplants before 2000, the importance of pretransplantation imatinib on transplantation outcome was not evaluated in this cohort. We evaluated time to transplantation along with donor source and degree of mismatch as a factor affecting outcome after receipt of matched or single mismatched transplant (Appendix Table A1, online only). Time to transplantation was considered as early (< 12 months), intermediate (12 to 24 months), and late (> 24 months). Patients receiving an early single class I (5-year overall survival, 51%; 95% CI, 56% to 67%) or DRB1 mismatched transplant (5-year overall survival, 55%; 95% CI, 26% to 82%) had survival estimates approaching those receiving a transplant at 12 to 24 months from 8/8 matched URD (5-year overall survival, 50%; 95% CI, 42% to 59%). Notably, a longer time to transplantation, even though still during chronic phase, was associated with greater decrement in 5-year survival in all URD transplant subsets than in MSD transplant recipients (Table A1).

DISCUSSION

In the current era, imatinib therapy has significantly altered the paradigm for selection of both nontransplantation and transplantation strategies. Initial reports of frequent cytogenetic responses with imatinib were published in 1999, and the drug was approved by the United States Food and Drug Administration in May 2001, followed by its widespread use.[13,14] This was followed by a dramatic decrease in allogeneic transplantation procedures for CML.[31] Currently, most centers now recommend allogeneic transplantation after failing imatinib or in later stages of the disease.[13,31]

Table 3. Multivariate Analysis: Relapse and TRM

Donor	No.	Relative Risk	95% CI	*P*	5-Year Incidence (%)
Relapse*					
HLA-identical sibling	3,422	1.00	—	—	14
8/8 matched URD	528	0.75	0.57 to 0.98	NS	12
7/8 class I mismatch	215	0.79	0.51 to 1.22	NS	11
7/8 DRB1 mismatch	37	0.90	0.33 to 2.43	NS	9
6/8 class I mismatch	128	0.50	0.24 to 1.0	NS	7
6/8 mixed mismatch (single DRB1 + single class I mismatch)	28	1.41	0.45 to 4.43	NS	12
7/8 DRB1 *v* 7/8 class I	NA	1.14	0.39 to 3.32	NS	NA
TRM†					
HLA-identical sibling	3,422	1.0			31
8/8 matched URD	528	1.45	1.24 to 1.70	< .0001	38
7/8 class I mismatch	215	1.98	1.59 to 2.45	< .0001	50
7/8 DRB1 mismatch	37	1.81	1.1 to 2.98	NS	48
6/8 class I mismatch	128	2.62	2.03 to 3.38	< .0001	58
6/8 mixed mismatch (single DRB1 + single class I mismatch)	28	3.80	2.36 to 6.13	< .001	67
7/8 DRB1 *v* 7/8 class I	NA	0.91	0.54 to 1.55	NS	NA

NOTE. Shown is the relative risk of relapse and TRM and associated 95% CIs.

Abbreviations: TRM, transplant related mortality; 8/8 matched URD, unrelated donor allele level matched at HLA-A, -B, -C, and -DRB1; 7/8 class I mismatch, single mismatch at antigen or allele level at HLA-A, -B, or -C; 7/8 DRB1 mismatch, single mismatch at allele level at HLA-DRB1; 6/8 class I mismatch, double mismatch at antigen or allele level at HLA-A, -B, or -C; 6/8 mixed mismatch (single DRB1 + single class I mismatch), double mixed mismatch, includes single mismatch at antigen or allele level at HLA-A, -B, -C, and single allele level mismatch at HLA-DRB1; NA, not assessable; NS, not significant.

*Model for relapse was also adjusted for each of the following significant variables: time from diagnosis to transplantation, T- cell depletion, sex mismatch, recipient race, and recipient age group.

†Model for TRM was also adjusted for each of the following significant variables: CMV match, time from diagnosis to transplantation, year of transplantation, recipient race, and recipient age group; it was stratified on sex mismatch.

Allogeneic transplantation, although curative, is associated with considerable mortality and morbidity with risks including GVHD, veno-occlusive disease of liver, infections, risks of secondary malignancy, and overall poorer quality of life.[32] URD compared with MSD transplants have been associated with both higher incidence of GVHD as well as higher TRM.[3]

The gold standard donor for allogeneic transplantation remains an MSD. Most prior studies evaluating comparative outcomes

Table 4. Multivariate Analysis: Grade II to IV Acute GVHD and Chronic GVHD

Donor	No.	Relative Risk	95% CI	*P*
Grade II-IV acute GVHD*				
HLA-identical siblings	3,422	1.00	—	—
8/8 matched URD	526	2.44	2.14 to 2.79	< .0001
7/8 class I mismatch	214	2.65	2.20 to 3.21	< .0001
7/8 DRB1 mismatch	35	2.64	1.69 to 4.13	< .0001
6/8 class I mismatches	128	2.81	2.22 to 3.56	< .0001
6/8 mixed mismatch (single DRB1 + single class I mismatch)	28	3.27	2.02 to 5.29	< .0001
7/8 DRB1 *v* 7/8 class I	NA	1.00	0.62 to 1.60	NS
Chronic GVHD†				
HLA-identical sibling	3,450	1.00	—	—
8/8 matched URD	508	1.97	1.71 to 2.26	< .0001
7/8 class I mismatch	204	1.64	1.32 to 2.05	< .0001
7/8 DRB1 mismatch	29	1.43	0.85 to 2.38	NS
6/8 class I mismatch	119	2.23	1.69 to 2.95	< .0001
6/8 mixed mismatch (single DRB1 + single class I mismatch)	22	1.33	0.60 to 2.99	NS
7/8 DRB1 *v* 7/8 class I	NA	0.87	0.5 to 1.5	NS

NOTE. Shown is the relative risk of grade II to IV acute GVHD and chronic GVHD and their associated 95% CIs.

*Model for grade II-IV acute GVHD also adjusted for each of the following significant variables: T-cell depletion and year of transplantation; it was stratified on Karnofsky score.

†Model for chronic GVHD also adjusted for each of the following significant variables: recipient age, total body irradiation–based conditioning regimen, sex mismatch, T-cell depletion, and year of transplantation; it was stratified on conditioning regimen.

Abbreviations: GVHD, graft-versus-host disease; 8/8 matched URD, unrelated donor allele level matched at HLA-A, -B, -C, and -DRB1; 7/8 class I mismatch, single mismatch at antigen or allele level at HLA-A, -B, or -C; 7/8 DRB1 mismatch, single mismatch at allele level at HLA-DRB1; 6/8 class I mismatch, double mismatch at antigen or allele level at HLA-A, -B, or -C; 6/8 mixed mismatch (single DRB1 + single class I mismatch), double mixed mismatch, includes single mismatch at antigen or allele level at HLA-A, -B, -C, and single allele level mismatch at HLA-DRB1; NA, not assessable; NS, not significant.

between MSD and URD transplant recipients have been limited by either lack of molecular typing in the URD or by small sample sizes.[3,4,33,34] We present results comparing outcomes in a large cohort of HLA matched and mismatched URD transplant recipients with those in MSD transplant recipients, while controlling for other major factors that may affect outcomes (disease, conditioning, disease stage, stem cell source). Majority of patients selected received transplants in the preimatinib era, with only 3% (n = 145; 89 MSD, 56 URD) receiving transplants after 2001, hence the impact of prior imatinib therapy was not evaluated.

Two recent studies from the CIBMTR[15,24] evaluated the impact of locus specific mismatching on outcomes. In both these analyses, mismatching at either HLA-A, -B, -C, or -DRB1 was associated with worse outcomes. The analysis by Lee et al[24] demonstrated that there was no difference between low- and high-resolution mismatch at a particular locus, hence the two were considered together for the purpose of this analysis. They also demonstrated no impact of mismatching at DP or DQ loci in their studies. We evaluated the impact of an DQ mismatch and found no independent influence on survival. However, a significant association was observed when HLA-DQB1 mismatching was present with additional HLA class I mismatches (data not shown); this observation confirms and extends those of previous studies which suggest that the additive effect of multiple mismatches is detrimental.[24,30]

In our analysis, overall survival after receipt of 8/8 matched URD transplant was closest to that after receipt of MSD transplant (63% *v* 55%) and declined with greater degrees of mismatch. Patients who received MSD and matched and mismatched URD transplants had similar risks of relapse; importantly, we did not observe lower risks of relapse with greater degrees of HLA mismatching. The risk of TRM was significantly higher in 8/8 matched URD than in MSD transplant recipients; the risk almost doubled in the presence of a single class I mismatch and more than tripled in the presence of mixed mismatches, yielding lower LFS in URD transplant recipients. LFS in 8/8 matched URD transplant recipients was closest to that in MSD transplant recipients but was progressively worse in the presence of mismatch in class I loci, due predominantly to higher TRM. T-cell depletion was used more frequently in URD transplant recipients, but was not frequent enough to allow comparison in each category of mismatch. It was, however, adjusted for in the multivariate models.

Although the current study did not address the outcomes in patients with more advanced stages of CML who received HLA matched or mismatched URD transplants, the results of the current analysis of CML CP1 patients suggest that overall transplantation outcome is defined by a balance of risks contributed by HLA disparity and by disease progression.

There have been few studies comparing outcomes in patients who received MSD and URD transplants. In an earlier report from NMDP[3], survival after receipt of MSD transplant was compared with that after receipt of URD transplant in patients with CML. Similar to our study, overall survival and disease-free survival (DFS) were only slightly (although significantly) lower in the cohort that received URD transplants, compared with the cohort that received MSD transplants. However, the population that received URD transplants in the earlier study was only serologically matched for HLA-A and -B, and matched by molecular typing only at HLA-DRB1. In that report, similar DFS in HCT involving MSDs and URDs was observed only in younger patients (< 30 years of age) undergoing transplantation within 1 year from diagnosis. In another study,[33] outcomes in 55 10/10 allele-matched URD (HLA-A, -B, -C, -DRB1, and -DQB1) transplant recipients were compared with those in 181 MSD transplant recipients for standard-risk hematologic malignancies, and similar outcomes were reported in the two cohorts. This study included 43 patients with CML (30 MSD transplant recipients and 13 URD transplant recipients) who were in either chronic or accelerated (n = 4) phase. The Australian Bone Marrow Transplant Registry reported a case control analysis of outcomes in 105 URD transplant recipients and 105 MSD transplant recipients with acute myelogenous leukemia. The URDs were serologically matched at HLA-A and -B, and molecular typing was used for HLA-DRB1 only. Five-year DFS was similar in the two cohorts.[34] In 1997, Szydlo et al[4] reported outcomes using IBMTR data in 2,055 MSD, partially matched related donor, or matched or mismatched URD transplant recipients. Matching, however, was defined only by serological criteria at HLA-A, -B, and -DRB1. Similar to our results, they reported a higher TRM and lower DFS in the cohort that received URD transplants.

This study confirms that in good-risk patients with CML in CP1 who lack a MSD, survival and LFS using 8/8 allele-matched URDs, although statistically slightly inferior, approach that of MSD HCT especially in the first year after diagnosis. When neither MSDs or 8/8 matched URDs are available, the judicious use of mismatched URDs requires balancing risks and benefits for individual patients, as graft versus leukemia potency was not afforded by HLA disparity.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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